REMARKS/ARGUMENTS

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Claim 28 has been amended to further clarify what Applicants have always regarded as their invention. Support for the recitation of an "isolated" antibody is found in the specification at, for example, page 311, lines 30-39.

Claims 28-32 are pending in this application.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph.

The remaining objection and rejections of Claims 28-32 under 35 U.S.C. §§101 and 112, first paragraph, and 35 U.S.C. §102(e) are addressed below.

I. Claim Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

Claims 28-32 stand rejected under 35 U.S.C. §101 because the claimed invention allegedly "is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 28-32 are also rejected under 35 U.S.C. §112, first paragraph, because allegedly "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility," and therefore "one of skill in the art clearly would not know how to use the claimed invention."

The Examiner acknowledges that DNA encoding for PRO1303 tested positive in a gene amplification assay, with the DNA being amplified over 2-fold in primary lung tumors and colon tumors. The Examiner asserts that although "the DNA encoding PRO1303 has diagnostic utility based on these results, the PRO1303 polypeptide does not" because there is allegedly "no information regarding level of expression, activity, or role in cancer" of the polypeptide. The Examiner quotes Pennica *et al.* and Konopka *et al.* to assert that "[i]ncreased copy number of DNA in a cancer or transformed cell does not necessarily result in increased level of expression of the polypeptide." Thus, the Examiner concludes that "even if amplification of a gene occurs

in a tumor cell, it does not mean that the mRNA or protein expressed from the gene is also amplified and thus suitable as a diagnostic marker for cancer, and that therefore "there is no substantial utility in using the protein for cancer therapy or screening for cancer therapeutics." (See pages 5-6 of the instant Office Action)

Regarding the adipocyte glucose/FFA uptake assay (Example 149), the Examiner asserts that the specification does not specifically assert how antibodies against PRO1303 would be used in any of the suggested treatments (see page 8 of the instant Office Action).. The Examiner further asserts that [b]ecause the instant specification, as filed, fails to disclose a specific role of PRO1303 in glucose and/or FFA uptake in adipocytes, one would have reasons to conclude that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. [9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the

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[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public"

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[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial'" utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the PRO1303 polypeptide and the claimed antibodies which specifically bind the PRO1303 polypeptide.

As discussed above, Applicants rely in part on the gene amplification data to establish patentable utility for the PRO1303 polypeptide. This data was first disclosed in Provisional Application No. 60/162,506 filed on October 29, 1999, the priority of which is claimed in the present application.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, which discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data.

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[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

The specification discloses that the nucleic acids encoding PRO1303 had ΔCt value of > 1.0, which is a **more than 2 -fold increase**, for primary lung tumors LT13, LT15, LT16; for lung cell line A549; and for the colon tumor CT16. Because amplification of DNA65409-1566 (PRO1303) occurs in various colon tumors, it is highly probable to play a significant role in tumor formation or growth, and antagonists (e.g. antibodies) directed against the protein encoded by DNA65409-1566 (PRO1303) would be expected to have utility in cancer therapy.

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1788 is ***a diagnostic marker of lung and colon***

cancer.

Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility for antibodies that specifically bind the PRO1303 polypeptide.

A *prima facie* case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* According to the quoted statement, "[i]n contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, a correlation between DNA amplification and over-expression of mRNA **was observed** in the case of WISP-1 (page 14722, col. 1).

Further, the Examiner cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to the amplification of the *abl* gene . . . ." Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Thus, the combined teachings of Pennica and

Konopka are not directed towards genes in general but to single gene or genes within a family and thus, their teachings have been misinterpreted in this rejection.

Accordingly, as stated above, since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance and the burden to provide further evidence of utility has not shifted to Applicants.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "... 62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers.

As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA.

While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, with the Examiner citing Pennica *et al.* (1998) and Konopka (1986), these

instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1303 gene, that the PRO1303 protein is concomitantly overexpressed.

Accordingly, the presumption of specific, substantial and credible asserted utility stands, and the burden to provide further evidence of utility has not shifted to Applicants.

Even if a *prima facie* case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility, as would antibodies that specifically bind to such a protein. In support, Applicants particularly draw the Examiner's attention to page 2 of the Declaration by Dr. Ashkenazi which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as

explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. (Pathology Associates Medical Laboratores, August (1999), copy enclosed). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Therefore, Applicants respectfully submit that the gene amplification data provided in the present application, as discussed above, are sufficient to establish a specific, substantial and credible utility for the PRO1303 polypeptide and antibodies that specifically bind it, for example, to be used as a diagnostic marker of human lung and colon cancer.

Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 28-32 under 35 U.S.C. §101.

The results of the adipocyte glucose/FFA uptake assay provide utility for the PRO1303 polypeptide

Applicants further rely in part on the adipocyte glucose/FFA uptake assay (Example 149, Assay #94) for support of patentable utility. This assay was first disclosed in International Application Serial No. PCT/US00/04342, filed on February 18, 2000, the priority of which is claimed in the present application.

The adipocyte glucose/FFA uptake assay is designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids

in adipocyte cells. By making such determinations, the assay identifies polypeptides that are expected to be useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is expected to be therapeutically effective. Examples of these types of disorders include obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1303 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1303 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 times (inhibitory) the uptake of the insulin control. As PRO1303 resulted in more than 1.5 times the uptake of the insulin control, PRO1303 tested positive as a stimulator of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay as described in Example 149 of the instant application was also well known in the art at the time of the effective filing date of the instant application. Similar assays were commonly used to identify potential anti-diabetic agents and to study the regulatory mechanisms of important molecules involved in fat cell metabolism.

For example, at the time of the effective filing date of the instant application, it was well known in the art that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents, such as troglitazone and pioglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al., Endocrinology*, 133(1):352-359 (1993) - copies enclosed). Both troglitazone and pioglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes.

Both compounds function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, at the time of the effective filing date of the instant application, vanadium salts were considered as a possible treatment for diabetes, and several clinical trials had already been performed. (Page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed). Using a rat adipocyte culture system similar to the system disclosed in the instant application, Goldwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 fold. This is further evidence that at the effective filing date of the present application one skilled in the art would have reasonably expected that molecules activating glucose uptake would find utility in the treatment of diabetes and related diseases.

In addition, the investigators in Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2): 551-558 (1998) - copy enclosed). Figure 1A shows the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggest that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and that the increase in leptin was closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect on leptin secretion of two well-known anti-diabetic agents, metformin and vanadium, which were known to enhance glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed).

The experimental data indicated that both metformin and vanadium increased glucose uptake and inhibit leptin secretion from cultured adipocytes.

Accordingly, Applicants respectfully submit that at the effective filing date of the instant application, one of skill in the art would have reasonably accepted that various compounds, such as PRO1303, that are capable of modulating glucose uptake have a substantial, practical, real life utility. The above-mentioned studies have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify therapeutic agents for treating diseases and conditions such as obesity, diabetes, and hyperinsulinemia. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO1303 based on the glucose/FFA uptake assay results disclosed herein.

The Examiner asserts that the specification did not indicate which asserted utilities correspond specifically to glucose uptake stimulation as opposed to glucose uptake inhibition. As discussed above, it was known in the art at the time of filing that agents which increased glucose uptake, such as troglitazone and pioglitazone, were useful in the treatment of diabetes. Treatment with vanadium salts, another agent which increased glucose uptake, was shown to lower glucose levels in hyperglycemic rats. Diabetes, hyperglycemia, and obesity were know at the time of filing to be closely linked conditions (see, for example, Sandouk, page 352). Thus one of skill in the art would have understood that stimulators of glucose uptake would be useful in the treatment of diabetes, obesity, and hyperglycemia.

The Examiner asserts that the specification does not indicate what, if any, of the utilities set forth correspond to stimulation of FFA uptake. The Examiner further asserts that stimulation of glucose and/or FFA uptake is actually three very different activities (stimulation of glucose uptake only, stimulation of FFA uptake only, and stimulation of uptake of both). Applicants respectfully point out that it was well known in the art at the time of filing that both glucose and FFA levels were associated with diabetes/hyperinsulinemia. See, for example, the discussion below of Fabris *et al.*, cited by the Examiner. Stimulation of uptake of either or both of glucose and FFA are not "very different activities" but closely related activities.

Accordingly, it is not necessary to specify which utilities correspond to FFA uptake versus glucose uptake, as the utilities are the same.

The Examiner asserts that "it is unclear how increasing uptake of FFA into adipocytes would treat obesity (or thus diabetes)." The Examiner cites Fabris *et al.* as teaching that "FFA-induced insulin resistance saves scarce glucose for central nervous system requirements, but this becomes counterproductive in obesity because it inhibits glucose utilization when there is no need to save it." (Page 8 of the instant Office Action). Applicants respectfully direct the Examiner's attention to the later discussion in Fabris *et al.*, where the authors make clear that FFA-induced insulin resistance is a result of high circulating FFA levels (page 604, col. 2). As the portion of Fabris *et al.* cited by the Examiner explains, this resistance leads to less utilization of glucose, which contributes to the development of obesity or diabetes. Thus Fabris *et al.* supports Applicants' assertion that decreasing circulating FFA levels, by increasing FFA uptake into adipocytes, will run counter to this trend and help in the treatment of obesity or diabetes. In addition, the reference by Santomauro *et al.*, cited by the Examiner, confirms that "lowering of elevated plasma FFA levels can reduce insulin resistance/hyperinsulinemia and improve oral glucose tolerance in lean and obese nondiabetic subjects and in obese patients with type 2 diabetes" (Abstract).

The Examiner further asserts that "the observed differences do not appear to be statistically significant, and the cutoff points appear to be arbitrary and there is no scientific basis for them." In support of this assertion, the Examiner cites Santomauro *et al.* Santomauro *et al.* teach that 56.5% decreases in FFA levels are statistically significant and correlated with physiological improvement. The Examiner states that "it is not clear whether 50% decreases are useful." Applicants respectfully submit that the difference between 56.5% and 50% is not large. Applicants further respectfully point out that the treatments in Santamauro *et al.* resulted in lowering FFA levels to below normal. One of skill in the art would expect that lowering FFA levels to only normal levels (requiring a decrease of only 41-44%) would also be useful.

The Examiner further states that "the observation that 56.5% decreases in circulating FFAs is significant and correlated with physiological improvements does not mean that a

doubling of uptake of FFAs by adipocytes will lead to the same decreases in FFAs." Applicants respectfully note that no evidence is provided for this assertion. The art indicates that *in vitro* uptake experiments with rat adipocytes actually underpredict the effects of treatment *in vivo*. For example, Goldwaser *et al.* demonstrated that vanadium ions increased glucose uptake in rat adipocytes *in vitro* by 4-5 fold, but lowered blood glucose levels in hyperglycemic rats *in vivo* by 5-7 fold (see Abstract).

Finally, Applicants respectfully remind Examiner that the standard for utility is not absolute certainty, but more likely than not. As discussed above, at the time of the effective filing date of the instant application, it was well known in the art that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents, such as troglitazone and pioglitazone. The art has also shown that agents which decrease circulating FFA levels are also useful in the treatment of disorders such as diabetes, hyperglycemia, and obesity. One of ordinary skill in the art would therefore find it more likely than not that an agent which increases uptake of glucose and/or FFA by adipocytes would also be useful in the treatment of disorders such as diabetes, hyperglycemia, and obesity. Accordingly, since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance and the burden to provide further evidence of utility has not shifted to Applicants.

Based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO1303 polypeptide and for antibodies that specifically bind to PRO1303. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

In view of the above, Applicants request the Examiner to reconsider and withdraw the rejection of claims 28-32 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph.

II. Claim Rejections Under 35 U.S.C. §102(e)

Claims 28-32 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Ni *et al.* (U.S. Patent No. 6,566,498). Ni *et al.* teach an isolated human secreted polypeptide

consisting of SEQ ID NO:6, which has two regions of 100% identity to SEQ ID NO:194, one region of 62 amino acids at the N-terminus, and one of 93 amino acids at the C-terminus of SEQ ID NO:194. The Examiner asserts that the two proteins are likely splice variants of each other and thus are very likely to have many exterior-exposed epitope domains in common. The Examiner further asserts that "because antigenic epitopes can be as low as 7 amino acids and preferably between 15 and 30 amino acids" allegedly "many of the antibodies taught by the reference which are directed against the protein of SEQ ID NO:6 would strongly cross-react with and specifically bind to the polypeptide of SEQ ID NO;194."

Applicants respectfully disagree and traverse the rejection.

First of all, Claim 28, and, consequently, those claims dependent from Claim 28, recites "an antibody that specifically binds to the polypeptide of SEQ ID NO:194." (Emphasis added). Applicants respectfully submit that the terms "specific binding" and "specifically binds" are well known terms of art in antibody technology. One skilled in the art understands that specific binding means that an antibody binds to a unique epitope within a target sequence. Example 16 of the U.S. Patent Office's Synopsis of Application of Written Description Guidelines clearly acknowledges that considering the routine and art-recognized methods of making antibodies, the well defined characteristics of the five classes of antibodies, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, the disclosure of an antigen implicitly discloses an antibody which binds to that antigen. This general determination is equally true to antibodies which "specifically bind" to a target antigen, since such antibodies can be identified by routine screening in routine competitive binding assays.

Therefore, Claim 28 and the claims dependent from Claim 28, carrying its recitations, clearly refer to an antibody that is able to bind to a specific epitope of the PRO1303 polypeptide *without* cross reacting with another epitope, including those found in the sequence disclosed in Ni *et al.* In view of this, the Examiner errs in assuming that the antibodies claimed in the present application would display significant binding to the polypeptide of Ni *et al.*, and thus overlap with the antibodies of Ni *et al.* As a result of the requirement of specific binding, the claims

pending in this application do not encompass antibodies that specifically bind to epitopes found in the polypeptide of Ni *et al.*

Applicants respectfully submit that a rejection under 35 U.S.C. § 102 can only be proper if the cited reference recites every element of the rejected claim. "For a prior art reference to anticipate in terms of 35 U.S.C. §102, *every* element of the claimed invention must be shown in a single reference." See *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). M.P.E.P. §2131 further provides, "A claim is anticipated only if *each* and *every* element as set forth in the claim is found, either expressly or inherently described in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as contained in the ... claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." The antibodies of Ni *et al.* do not bind specifically to SEQ ID NO:227, as recited in the claims, and therefore the antibodies of Ni *et al.* do not anticipate the claimed antibodies.

Clearly there exist specific epitopes in the SEQ ID NO:194 protein that are not found in the Ni protein. Applicants note that, as shown in the sequence alignment provided by the Examiner in the instant Office Action, SEQ ID NO:194 contains a 93 amino acid region in the middle of the protein that is not present in SEQ ID NO:6 of Ni *et al.* Thus this 93 amino acid region of SEQ ID NO:194 contains numerous epitopes not found in the protein of Ni *et al.* Accordingly, one of ordinary skill in the art would readily understand what is meant by antibodies which specifically bind to SEQ ID NO:194 (and not, for example, to the polypeptide of Ni *et al.*). Such antibodies would clearly include, for example, antibodies that bind to epitopes found within the amino terminal half of SEQ ID NO:194.

Furthermore, as is well known in the art, an antibody generally recognizes only a small region on the surface of a large molecule. (See Janeway *et al.*, *Immunobiology*: *Antigen Recognition by B-cell and T-cell Receptors*, page 102, 2001; copy enclosed). The structures generally recognized by the antibody are located on the surface of the protein and such sites are likely to be composed of amino acids from different parts of the polypeptide chain that have been brought together by protein folding. *Id.* Epitopes of this kind are known as conformational or

discontinuous epitopes because the structure recognized is composed of segments of the protein that are discontinuous in the amino acid sequence of the antigen but are brought together in the three-dimensional structure. *Id.* Most antibodies raised against intact, fully folded proteins recognize discontinuous epitopes. *Id* at 102-103 (emphasis added). For this reason, the binding sites for the claimed antibodies cannot be simply predicted based on the linear sequence homology between the amino acid sequence of the present invention and that of Ni.

It is well understood in the art that protein folding is a complex process and that a protein's conformation cannot be predicted simply based on the primary amino acid sequence. Given the limited degree of sequence identity, the three dimensional structure of the PRO1303 polypeptide cannot be predicted by the sequence of Ni. Since it is unlikely that the PRO1303 polypeptide would have the same three-dimensional protein structure as the sequence of Ni, most likely there will be discontinuous epitopes in the PRO1303 polypeptides that are missing in the Ni protein, for example, at sites where regions from the amino terminal half of the PRO1303 polypeptide sequence interact with the overlapping regions. For this reason, one of skill in the art would understand that specific epitopes of the PRO1303 polypeptide may include residues from the overlapping regions, as part of a non-linear epitope.

One of ordinary skill in the art would further understand how to make and use such antibodies. The specification provides methods to determine whether an antibody specifically binds to epitopes possessed by SEQ ID NO:194. Routine methods of determining antibody binding specificities, including immunoprecipitation, or competitive binding assays such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA), are disclosed in the specification at, for example, page 373, lines 32-35. Methods of determining the binding affinities of antibodies using Scatchard analysis are disclosed at page 373, lines 35-36. In addition, a method of using competitive binding assays to determine if a peptide shares an antigenic determinant for a particular antibody with a PRO polypeptide is disclosed in the specification at page 488, lines 25-29.

Furthermore, at the time the invention was made, it was well known in the art that antibodies directed against a target antigen can be raised and isolated using commonly known

methods. Thus, for example, antibody phage display, which was known in the art at the priority date of the present application, is a powerful technique for selecting antibodies. An antibody phage library typically consists of the variable regions of heavy (V_H) and light (V_L) chains of antibodies, which are randomly combined and linked together by a polypeptide linker to form a single-chain fragment (scFv). These scFvs are usually fused to a minor coat protein of bacteriophage M13, pIII, resulting in phages displaying antibody fragments. The display of scFvs on a filamentous phage offers the possibility to select phage antibodies by several rounds of a technique called on an immobilized antigen. The large synthetic libraries available in the art can be used to select antibodies against any given antigen, and allow the selection of antibodies that selectively bind one antigen and do not bind any other antigen. For further details, see, *e.g.* Winter *et al.*, *Annu. Rev. Immunol.* 12:433-455 (1994) (copy enclosed).

As the specification provides simple, art-recognized methods, described in the preceding paragraphs, for determining those antibodies covered by the claims, the meaning of the claims is clear, and one of skill in the art would readily understand how to make and use the claimed antibodies.

Accordingly, Appellants respectfully submit that Ni *et al.* is not prior art under 102(e) and request the Examiner to reconsider and withdraw the present rejection.. Applicants further submit that the pending claims are fully enabled by the disclosure of the present application and general knowledge in the pertinent art at the effective filing date of this application.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2830 P1C15**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 5, 2005

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